Remarks

Claims 28, 29, 30 and 32 are under consideration. The amendments to Claim 28 find support in at least original Claims 16 and 20. Claim 28 has been amended for the purpose of expediting prosecution by conforming it to the scope of what has been examined. Claim 31 has been cancelled without prejudice. Claim 32 finds support in original Claim 21. In a telephone discussion on Dec. 22, 2006, the Examiner indicated that once a patentable generic claim had been established, claims with further limitations (such as the claims to hydroxyurea) might be allowable. If counsel has misunderstood, then the applicants agree to cancel Claims 29 and 30. A terminal disclaimer to overcome an obviousness double-patenting rejection is included. A terminal disclaimer to overcome a provisional double-patenting rejection, together argument, and with an authorization to charge an additional fee in the event this provisional rejection is made final.

Background

This application is a CIP of an allowed patent for a vaccine with unique properties, comprising DNA and mannosylated polyethylenimine. The present application arose when a safety test for the vaccine yielded surprising results that showed that the vaccine could be used to treat already-existing infection. Due to safety concerns about any use of DNA encoding any part of a virus, the vaccine, which is a DNA encoding at least one retroviral protein, was tested in animals having compromised immune systems due to late-stage AIDS. It was felt that any safety issues of the vaccine would be magnified by the poor condition of the animals' immune systems. Under these conditions, the vaccine was not expected to have a therapeutic effect. It was found, however, that if viral replication could be suppressed with drug treatment, the vaccine could be used, and use of the vaccine resulted in an improved immune response. The present invention has a great advantage because it extends vaccine treatment to a group of patients thought to be untreatable.

Claim 28 quotes all the limitations of Claim 1 of the parent patent. This was done to overcome any formal objections the claim language, and also to place the claims in such condition that any limitations with respect to drug treatment are added limitations that narrow the scope of the claims with respect to the claims that have already been allowed. The Examiner made a restriction requirement in the case with respect to the added limitations, and made it final. The amended Claims conform to the restriction.

Election/Restrictions

The Examiner states that Claim 28-32 comprised inventions nonelected with traverse in the paper filed 5-12-03. The Examiner states that a complete reply to the final rejection

must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The original restriction/election was limited to administering the patentably distinct combination of ddI (an RT inhibitor) and indinavir (a protease inhibitor). The restriction is said to be maintained because i) RT inhibitors, protease inhibitors and hydroxyurea have different structures and functions, ii) the species of RT inhibitors in claims 29 and 31 have different structures and inhibit RT using different mechanisms, iii) the species of protease inhibitors in claims 30 and 31 have different structures and inhibit protease using different mechanisms, and ii) the burden required to search administering all combinations of RT inhibitor species and protease inhibitor species together with administering DNA encoding an immunogenic retroviral protein would be undue. Thus the Applicants' request for an expanded search after filing an RCE has been denied.

The Examiner states Claim 32 was withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no examined generic or linking claim.

Claims 28-31 were said to be under consideration only as they relate to administering antiretroviral drug therapy comprising ddI (an RT inhibitor) and indinavir (a protease inhibitor) until viral replication is suppressed, and then administering DNA encoding an immunogenic retroviral protein operably linked with a promoter. Applicants' request for searches of other aritiviral drugs has been denied.

Response – Restriction/election Requirement

In response the Applicants note that all but Claims 28 and 32 have been cancelled, and Claim 28 has been amended to conform to the scope of the restriction requirement. This application is a CIP of USPN 6,420,176. The Claims had already been amended to quote all the limitations of Claim 1 of the parent patent. Claims 28 and 32 contain further limitations. The Examiner has admitted there is no prior art against the Claims.

Specification

The Examiner has not accepted the amendment to the paragraph bridging pg 22-23 and pg 23-24, and it is hereby submitted as required, using the version filed 3-11-04. The Examiner states that the amendment filed 3/11/04 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material that is allegedly not supported by the original disclosure is as follows: the specification does not support the changes made to the paragraph bridging pg 22-23 or the paragraph bridging pg 23-24.

Response – Specification

In response, the Applicants have resubmitted the amendment as required.

Claim Rejections – 35 USC § 112

New Matter

Claims 28-31 had been rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. The claim(s) are said to contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner states that the phrase, "at least one immunogenic retroviral protein" in claim 28 is new matter, alleging that support cannot be found in claim 1 as asserted by the applicants.

The Examiner states that the limitation of "BMS 23632" in Claims 30 and 31 was not contemplated in the specification as originally filed. The Examiner does not note the applicants' citation to that specific material at page 24, line 8 in the application, but states that it is not readily apparent that BMS 23632 was available at the time of filing.

Response – New Matter

The applicants note that, in an effort to expedite prosecution of this CIP, the Claims were amended to quote all the limitations from Claim 1 of the parent patent. The Claim finds further support as follows.

The application discloses at page 10 lines 24-26, that one of the objects of the invention is "to provide a means of stimulating both humoral and cellular immune responses to the **protein** product of the transferred genetic material." The application discloses at page 11, lines 5-8 that an "advantage of the present invention is that it can utilize any type of DNA... including plasmid DNA encoding immunogens like ...**viral proteins**.... At page 16, line 15: ("If the purpose of the gene transfer is to induce an immune response, then the genetic material must express **one or more immunogenic proteins**..."). Reverse transcriptase dependent viruses are suggested at least at pag 16, lines 21-22. **Retroviruses** are particularly mentioned among the list of choices on page 17, line 5. The experiments are all directed toward control of replication of HIV, and HIV is disclosed to be a **retrovirus** at page 44, line 3.

With respect to the objection to BMS 23632, the material has been deleted from the Claims.

Claim Rejections 35 USC § 112 – enablement – Indinavir and ddI

Claims 28-31 have been rejected under 35 USC 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which is pertains, or which it is most nearly connected, to make and/or use the invention for reasons of record.

The Examiner admits that administering an antiretroviral drug therapy comprising ddI and Indinavir until retroviral replication is effectively suppressed is considered enabled

in this application not based on the text of the application as pointed out by the applicants, but because somebody else, Finzi taught administering a reverse transcriptase inhibitor and a protease inhibitor suppressed retroviral replication (Finzi et al. Science. Nov. 14, 1997, Vol. 278, pg 1295-1300).

Response – Claim Rejections 35 USC § 112 – enablement

Claim 28 has been amended to be enabled as admitted by the Examiner.

Claim Rejections 35 USC § 112 – enablement – requirement for "Therapeutic Immune Response"

In the event this rejection is being maintained, the applicant respectfully requests a telephone call from the Examiner, to expedite the filing of an RCE.

Claims 28-31 are said to require administering DNA encoding an immunogenic retroviral protein after administering the antiretroviral drug therapy. The Examiner says that the sole disclosed purpose for administering DNA encoding an immunogenic retroviral protein is to induce an immune response against the retroviral protein that is therapeutic (pg 2, lines 14-19). Therefore, the Examiner states that the step of administering DNA encoding an immunogenic retroviral protein must be fully enabled for using the DNA to obtain a therapeutic immune response against the "immunogenic retroviral protein". However, the Examiner states that the specification does not enable using DNA encoding an immunogenic retroviral protein to induce a therapeutic immune response against a retrovirus in a host.

The Examiner takes the position that Claims 28-31 are not enabled because the structure of the DNA encoding an immunogenic retroviral protein that provides a therapeutic immune response against the retroviral protein is not enabled.

The Examiner states that, according to another reference, not the inventor's disclosure, that the state of the art at the time of filing was that the combination of vector, promoter, route of administration, level of expression and target tissue required to obtain a therapeutic or prophylactic effect using gene therapy was unpredictable. Miller of record (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for in vivo gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances... targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain of record (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art that show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma of record (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal of record (1995, Science, Vol. 270, page 404410) also reviews various vectors known in the art and indicates, "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be

regulated" (page 409).

The Examiner says that the state of the art regarding treating retroviral infection was unpredictable, that Stricker of record (Medical Hypotheses, June 1997, Vol. 48, pages 527-9) teaches that attempts to develop a vaccine against HIV have been unsuccessful because HIV vaccines do not neutralize HIV (pg 527, last paragraph through all of pg 528). Overall, a lack of understanding about protective immunity to HIV in humans, the sequence variability of HIV and the rapid replication of HIV contribute the ineffectiveness of vaccines against HIV (Bangham of record, Nov. 29, 1997, Lancet, Vol. 350, pages 1617-1621; page 1617, top of col. 1).

The Examiner admits that the specification teaches a complex comprising i) manosylated PEI and ii) DNA encoding an immunogenic HIV protein operably linked to a promoter. The Examiner remarks that administration of the complex to a host after drug therapy was followed by an increase in CD4 cells then a decrease in CD4 cells (pg 53).

The Examiner states that the specification does not provide adequate guidance for one of skill to use DNA encoding an "immunogenic retroviral protein" to induce an immune response capable of treating a retroviral infection. The Examiner discounts the results described in the specification as being not therapeutic because the overall result does not result in a net increase in CD4 cells. In addition, the Examiner states that it cannot be concluded that the DNA encoding a retroviral protein caused the initial increase in CD4 cells because the experiment did not include controls - animals that did not receive drug therapy or the gene complex. The Examiner says the specification does not provide adequate guidance indicating the increase in CD4 was caused by an immune response to the retroviral protein encoded by the DNA - the drug therapy could have caused the increase in CD4. The Examiner states that the specification did not teach treating animals that were already infected (not true) or challenging the animals after they were given DermaVir. For administration of DNA encoding a retroviral protein to induce a therapeutic immune response, the specification must overcome the unpredictability in the art by adequately describing the structure of the foreign genetic material" used, the dosage and route of administration that results in a therapeutic effect or immunization." Without such guidance it would require one of skill in the art undue experimentation to overcome the unpredictability in the art regarding gene therapy and retroviral therapy to determine the combination of elements required to obtain a therapeutic or prophylactic effect against retroviral infection using "DNA". Therefore, the specification is said to not enable "treating retroviral infection" using "**DNA**" as claimed.

Response to Claim Rejections 35 USC § 112 – enablement – Requirement for "Therapeutic Immune Response"

In the event this objection is not withdrawn, the Applicant requests a phone call from the Examiner to expedite filing of an RCE. The applicants note that this issue was resolved in the parent application, and that the present application quotes Claim 1 of the parent application, with added limitations. This question has been settled in the parent case, and the applicants are entitled to rely on the text of the parent as being enabled for the language found in the claims of the parent.

The claimed invention relates to a material disclosed in the parent application that was originally proposed as a vaccine, and a method of using that material to treat active infection. The text from the parent application, which was incorporated in full in the current text, described the vaccine. The present application contains additional disclosure about drug therapies and experiments that demonstrate how to use the vaccine in combination with

drug therapy to get a therapeutic result in a population that had previously been thought to be untreatable, i.e., animals whose immune systems had supposedly been destroyed. This is a therapeutic effect – animals that already were exhibiting signs of AIDS, and who were beginning to fail on the very best prior art drug treatment were treated with drugs to suppress viral replication and then the claimed complex. They subsequently exhibited control of virus replication as well as significantly improved survival time. Given these results, the CD4 count, which fluctuated, and which was associated in at least one case with a higher viral rebound, was not a good marker for disease control (page 53, lines 7-17) a result that is consistent with the findings of at least one other research group (Havlir). In addition, the inventors disclose a new result: the experiments show that the claimed invention can be used as treatment for active infection in animals that are failing drug treatment. This runs counter to the original sense of the teaching in the parent application, which is that the vaccine could be used as a therapy, provided that suppression of viral replication occurs either before the immune system had been substantially damaged, or long enough to allow the immune system to recover. (page 20, lines 27-31 of the present application quotes the language of the parent).

Claim Rejections 35 USC § 112 – enablement – Claims confined to Examples

> The Examiner points to a portion of the specification, which states:
> The comparison of the rate of viral load rebound among those animals undergoing STI-HAART early after infection (Lori, F. et al. Control of SIV rebound through structured treatment interruptions during early infection. Science 290, 1591-1593. (2000)), those initiating STI-HAART during AIDS, and the same animals treated with STI-HARRT plus DermaVirSHIV revealed an interesting pattern. The rate of viral rebound during consecutive HAART interruptions, that was unchanged before the initiation of vaccine therapy, decreased sharply after vaccination, and became remarkably similar to that observed in the animals treated with STI-HAART early after infection (Fig. 14). These results suggest that DermaVirSHIV therapy can improve the control of virus replication during interruption of HAART. (pg 53, lines 18-27)

The Examiner states that HAART therapy as described in Lori of record (2000) is PMPA (tenofovir, and RT inhibitor) ddI (didanosine, and RT inhibitor) and hydroxyurea (pg 1591, col. 3, lines 10-18). STI-HAART is structured treatment interruptions of HAART therapy.

The Examiner agrees that the interrupted administration of PMPA, ddI and hydroxyurea followed by administration of DermaVir_{shiv} (AIDS(DermaVir)) in Fig. 14 shows decreased viral rebound as compared to interrupted administration of PMPA, ddI and hydroxyurea (AIDS(HAART)).

The Examiner states that the claims are being considered as they relate to administering ddI and indinavir followed by a gene complex; however, the Examiner takes the position that the example is limited to administering PMPA, ddI and hydroxyurea followed by a gene delivery complex. The Examiner states that the combination of administering drugs plus DermaVir_{shiv} in the example does not correlate to administering

ddI and indinavir plus DermaVir$_{shiv}$. The Examiner states that the specific combination of DermaVirshiv with PMPA or hydroxyurea may have decreased viral rebound in the example. The Examiner speculates that perhaps the combination of two different RT inhibitors in the example with DermaVir$_{shiv}$ decreased viral rebound (PMPA and ddI have different structures and different mechanisms of action (see DeClerq, Current Medicinal Chemistry, 2001, Vol. 8, pg 1543-1572; para bridging pg 1553-1554; nucleotide v. nucleoside analogs; "PMPA only needs two phosphorylation steps to be converted to the active metabolite"). The Examiner states that the examples does not use indinavir or any other protease inhibitor. The Examiner states that the decreased rebound effect in the example may be a synergistic effect obtained only in the presence of PMPA, PMPA and ddI or hydroxyurea. Therefore, according to the examiner, one of ordinary skill in the art would not expect DermaVirshiv to decrease viral rebound after administering ddI and indinavir based on the example, which is limited to administering ddI, PMPA and hydroxyurea followed by DermaVir$_{shiv}$.

The Examiner argues further that the claims encompass administering continuous HAART followed by DermaVirsHIv; however, the Examiner states that the example is limited to interrupted HAART. The Examiner states that the specification does not correlate decreasing viral rebound obtained by interrupting HAART followed by DermaVir$_{SHIV}$ with expected results obtained by administering continuous HAART plus DermaVir$_{SHIV}$ (i.e. the virus does not rebound during continuous HAART). Therefore, the mode of drug delivery in the example does not correlate to any mode of delivery as broadly encompassed by claim 21.

The Examiner states that the claims encompass delivering any gene complex comprising DNA encoding any immunogenic retroviral protein; however, the example is limited to DermaVir$_{SHIV}$.

The Examiner points to a portion of the specification, which states:

> DermaVir$_{SHIV}$ is a glucose-water solution containing a plasmid DNA as an active ingredient and polyethylenimine-mannose (PEIm) as an adjuvant (See Example 12). One therapeutic application contained 0.1 mg DNA capable of expressing all but the integrase protein of the Simian-Human Immunodeficiency Virus (SHIV). DermaVir$_{SHIV}$ was formulated to transduce Langerhans cells located in the epidermis and it was applied on the surface of the skin of the animals. We have shown that these Langerhans cells are triggered to migrate to the lymph nodes, mature to dendritic cells and present SHIV antigens to naïve T cells. After SHIV-specific activation of naïve T cells in the lymph nodes, DermaVir$_{SHIV}$ initiated potent SIV-specific T cell-mediated immune responses in uninfected monkeys (See Example 12)" (pg 52, lines 1-9).

On this basis, the Examiner states that the specification does not correlate with the results obtained with DermaVir$_{SHIV}$, which expresses all retroviral proteins except integrase, to any DNA encoding any immunogenic retroviral proteins except integrase, to any DNA encoding any immunogenic retroviral proteins, such as gp120. The expression of all retroviral proteins may be essential to induce the proper immune response and decrease viral rebound. (see pg 52, lines 1-9).

The Examiner states further that not only is the gene complex itself much narrower in scope than the gene delivery complex claimed, the mode of delivery described in the specification is limited to dermal administration.

The Examiner states that, in conclusion, the example on pg 53 is much narrower than claim 21(sic) in the types of drugs administered, the mode of delivery of the drugs, the gene complex being delivered and the mode of delivery of the gene complex. Decreasing viral rebound after interrupting two RT inhibitors and hydroxyurea cannot even be extrapolated to administration of ddI and indinavir because the combination of drugs in the example may have allowed DermaVir$_{SHIV}$ to function.

Response -- Claim Rejections 35 USC § 112 – enablement – Claims confined to Examples

The Examiner has stated that the Example in the Specification does not correlate to the specification, so that the Claims are not enabled, apparently taking the position that the applicants are not entitled to claim the use of any given drug unless it is specifically supported by name (rather than class or function) *in an example*. However, this rejection does not take into account the full disclosure of the application, which must be taken as a whole. As stated at page 24, lines 24-25, the Examples are presented for the purpose of illustrating the practice of the invention, and do not limit either the invention, or the Claims. The application discloses that certain classes of drugs suitable for use in the present invention starting at page 21, line 17. This includes highly active antiretroviral therapy, described at page 21, lines 21-24: "Highly active antiretroviral therapy a name commonly used in the field of HIV infection to mean combinations of three or more drugs, including at least one reverse transcriptase inhibitor and one protease inhibitor, or any combination of the drugs described below might be used according to the present invention for treatment of HIV infection." Drug classes and individual drug names are clearly disclosed and enabled in the application text. The drugs known to suppress viral replication, as claimed, are clearly disclosed by both class and function at least at page 21, lines 17-25. The names of various drugs that can be included in the claimed combinations are disclosed at least at pages 21, line 26-page 24, line 20, and the original Claims as filed.

To the extent the Examiner's objection is based on the use of drugs different from the preferred human drugs and a DNA different from a human DNA, it is noted that a detailed discussion of the selection of the rhesus macaque model and pathogenic SHIV begins at page 43, first full paragraph. The researchers explain the technical background that guided them to chose to use a rhesus macaque model, and selected the drugs, and modified the vaccine for the purpose of providing a model that correlated to treatment in humans. The experiments confirm that the course of disease and drug treatment resembles that of humans. A direct correlation between the monkey model and results in humans with respect to drug treatment is noted at page 49, line 22-23. It is disclosed that the evolution of the disease in this model is similar to that in humans, at page 50, lines 18-19 and so was the response to treatment interruptions, at page 51, lines 4-7. The application notes at page 51, lines 9-11, that "these results further confirm the similarity between clinical evolution of the disease in animals and in humans." Further, the irregular response of CD4 counts during treatment interruptions also correlates with results found by others in humans at page 53, lines 7-17. This application provides experimental proof that the animal model is

appropriate and useful to illustrate the invention, and that experiments using the model have been both published and correlated with articles by others in various peer-reviewed journals, so one of ordinary skill in the art would recognize that the experiments do correlate with human treatment.

Further comments about the Applicants' Argument by the Examiner

Applicants argue, "the examiner appears to be operating under a misunderstanding of the applicable law. The disclosure in a patent application is required to enable one skilled in the art to make or use the claimed invention. There is no requirement for an inventor to conform to somebody else's idea of what might be required. Further, all the disclosure of the application must be relied upon for enablement of the invention and not just the specific examples used to illustrate the invention. The Claims are not limited merely to the specific materials used in the Examples. In addition, the Examiner appears to be operating under a misunderstanding of fact: a therapeutic immune response is unquestionably demonstrated in the text."

The Examiner takes the position that the applicants' argument is not substantial. The examiners rejection is said to review the teachings of the specification in context of the Examples and the teachings in the art at the time of filing and correlated them with the Wands factors of enablement. The Examiner says that the applicants have not pointed to one error in the examiner's logic or in the analysis of the law or the teachings in the specification. Applicants argue Miller, Deonarain, Verma, Crystal, etc. "were wrong, and that is why they are not the inventors of the present case." Applicants' argument is not substantial and is illogical. Applicants' logic that Miller, Deonarain, etc. were not the inventors of the present case because they "were wrong" is flawed, and the reasons why they were not inventors are irrelevant. Applicants' have not provided to any evidence that those numerous skilled artisans at the time of filing were wrong. Applicants arguments in the last 14 lines of pg 9 of the response are not persuasive because they discuss fluctuations in CD4 cell numbers without discussing how the DNA contributed to a therapeutic immune response or specifically to CD4 cell numbers. The basis of the rejection is that the specification does not provide adequate guidance indicating the DNA contributed to any therapeutic effect.

Applicants' argument in the first paragraph of pg 10 regarding the animals being infected already is moot. Applicants do not discuss how the specification enables one of skill to use the DNA to induce a therapeutic immune response - the basis of the rejection.

Applicants argue controls died long before this set of experiments were begun (pg 10, 2). Applicants' argument is moot. "This set of experiments" (i.e. Example 13) needed their own set of controls. Specifically, a group that was capable of determining whether the DNA contributed to the increased CD4 counts. Without evidence to the contrary, given the lack of DNA vaccines capable of increasing CD4 counts, the DNA administered by applicants did not contribute to the increased CD4 counts. Applicants fail to describe any logic as to how one of skill could conclude without the proper control that the DNA contributed to the increased CD4 and was not solely caused by the anti-retroviral therapy.

The Examiner states that the Applicants' argument in the paragraph bridging pag 10-11 discusses the examiner's position regarding the lack of correlation between the antiretroviral drugs in Example 13 and ddI and indinavir currently under consideration in the claims. Applicants state: "[t]his possibility has been eliminated by the progression of the experiment.: "This possibility" appears to refer to the examiner's position; however, the meaning of applicants' statement is unclear. It cannot be determined what has been "eliminated by the progression of the experiment." PMPA or hydroxyurea used in Example 13 do not correlate to ddI and indinavir as currently under consideration because

they have differne structures and different modes of action, and because they may act synergistically with the DNA while ddI and indinavir may not.

The Examiner states that the scope of the gene complex in parent application 6,420,176 is moot because the claims in '176 are directed to the gene complex, not a method of treating a retroviral infection using the gene complex. The gene complex of '176 can be used to transfect cells in vitro and is not limited to being used to treat a retroviral infection as now specifically claimed.

Response to the Further Comments

With respect to the Examiner's comments dismissing the Applicants' arguments, it is noted that the claim language incorporates all the limitations of Claim 1 of the parent case. In response to the Examiner's comment that the scope of the claims in the parent case is moot, the applicants point out that these issues all relate to the description of the vaccine, and were settled in the parent case. The text of the parent case has been incorporated in full in the present application. It is not unreasonable to allow issues that have been settled to remain settled.

The applicants note that the applicants have stated the applicable law, and that the Group 1600 requirement for information related to the technology of others is not the applicable law. The arguments presented by the Applicants are consistent with the laws and regulations governing the entire United States Patent and Trademark Office. The citation of others' notions about what would be needed to meet the goals of their research is speculation as to what it would take to make another set of potential inventions work another way. This is not the standard for enablement, which is that the disclosure must enable one skilled in the art to make or use the claimed invention, not another, unrelated invention. The present inventors did it a different way, with different materials. Their obligation is to describe how they do it, not how somebody else might do something else.

With respect to the remark that the specification does not provide adequate guidance indicating that the DNA contributed to any therapeutic effect, the applicants note that the application discloses that this application includes *in vivo* results: animals were treated with progressively more sophisticated drug therapy until the best available therapy began to fail. Then, the vaccine was added to the therapy, and CTL responses were resurrected in deathly ill animals, so that they had enhanced control of viremia and lived longer.

To the extent that Examiner's statement that the Applicants must discuss how the DNA contributed to a therapeutic immune response or specifically to CD4 cell numbers is a requirement for an underlying mechanism of action, the applicants note that it is a requirement for speculation. The examples show that very ill animals treated with the claimed invention improved their immune response. The application discloses how to make

and use the applicant's invention to get a demonstrated benefit. No further discussion of underlying mechanism is required.

The Examiner's statements with respect to the "lack" of controls are not true. This series of experiments is part of a long-running project involving a cohort that originally included infected, untreated animals. Those animals died quickly. See the application at page 50, lines 3-5. From the original cohort, 14 animals died prior to the study comparing continuous HAART and STI-HAART, and 3 more died during the protocol approval period. The remaining 7 were randomized into 3 receiving continuous HAART and 4 receiving STI-HAART. All the animals receiving continuous HAART died, similar to the experience in humans. See page 50, lines 12-22. The animals in the STI-HAART group had a better survival rate, but then they began to fail, as well. They began to show increasing viral load and viral rebound during treatment cessation periods See page 51, lines 12-18. This remnant population was used to test the vaccine. The application discloses that the inventors were interested in controlling viral replication. See page 51, lines 17-21, where the inventors disclose that they decided to study the potential benefit of vaccination in hopes of initiating specific T cell immunity, which has been previously shown to control virus replication in long-term non-progressors. This experiment had a number of "control" groups that were treated with progressively sophisticated regimens. Untreated animals were compared to those with continuous HAART. Untreated animals (controls) died first. Those on continuous HAART were then randomized into two groups: continuous HAART and STI-HAART. In that phase, the "continuous HAART" group served as controls. All of the animals in the continuous HAART group died. All that were left were animals on STI-HAART. That group was randomized, and the "STI-HAART" groups served as controls against those given the vaccine. Compared to the STI-HAART group, the vaccinated group showed improved control of viral replication and longevity.

Given this history, it is clear that the vaccine, referred to by the Examiner as "DNA," is clearly associated with an improvement over STI-HAART, HAART, and no treatment. These results clearly were not obtained by antiretroviral therapy alone, because the most sophisticated version of the antiretroviral therapy had already begun to fail before the vaccine was administered. One of ordinary skill in the art would readily conclude that the vaccine was responsible for the improvement, because it was the only element of the experiment that was varied at that time.

The application does disclosed that CD4 results fluctuated and that a lower level of CD4 cells was associated with better control of viral rebound, a result that was also found by other researchers. This is simply a finding that a surrogate marker does not readily predict either control of viremia or extended lifespan. This finding does not in any way

negate the experimental results. Indeed, the inventors disclose that other researchers have found the same effect in humans (page 53, lines 7-17). In light of all this data, it is not understood how an enablement rejection can be said to lie against this application, unless an examination standard is being applied that is different from those applied to the other technical arts.

Whether patents are allowable in a given particular field of art is not a question of Patent and Trademark Office discretion but of law, and examiners have no discretion to deny patents to inventions meeting the statutory criteria. Animal Legal Defense Fund v. Quigg, 18 USPQ 2d 1677, 1685, Fed. Cir. (1985). The standard for enablement focuses on the person skilled in the art, Radomex, Inc. v. Scopus Corp., 7 USPQ2d 1050 (Fed. Cir. 1988) rather than the general public. For this reason, a specification is not required to teach what is known in the relevant art. Lindeman Maschinenfabrik GmbH v. American Hoist & Derrick Co., 221 USPQ 481, 489 (Fed. Cir. 1984). Human clinical trials are not required, In re Brana, 34 USPQ2d 1436 (Fed. Cir. 1995) and the PTO should not confuse the standard for patentability with the standard for FDA approval id., at 1442.

The enablement/utility objections find their application in discouraging filings based on hypothetical examples and in cases of fraud, such as In re Oberweger, (baldness cure) 47 USPQ 455, 457 (CCPA 1940), but not more credible cases. See USPN 4,139,619 issued February 13, 1979 for a method of stimulating hair growth by topical application of minoxidil, and note that the text refers to another patent for the method of making the active ingredient in a series of formulations, and for experimental support. The present application contains clear experimental support for the amended Claims, and therefore the present objection should be withdrawn at this time.

The Examiner's comment with respect to the "lack of correlation" based on the different drugs involved, is inconsistent with the teachings of the application. The application teaches the use of known antiretroviral drug therapies in combination with the inventors' vaccine. The experiments use drugs disclosed to be known and effective, and listed by name in the application. The experiments do correlate with the text of the application. To the extent that the Examiner's objection is based on the use of PMPA, it is noted that this is an animal model, and that adjustments were made in the infectious virus, the vaccine, and the vaccine and drug therapy to obtain a model that provides useful correlations to the human disease condition. A detailed discussion of the selection of the rhesus macaque model and pathogenic SHIV begins at page 43, first full paragraph. A

direct correlation between the monkey model and results in humans is noted at page 49, line 22-23. The evolution of the disease in this experiment with these animals is noted to be similar in this model and humans at page 50, lines 18-19, and so is the response to treatment interruptions at page 51, lines 4-7. The application notes at page 51, lines 9-11, that "these results further confirm the similarity between clinical evolution of the disease in animals and in humans." Further, the irregular response of CD4 counts during treatment interruptions also correlates with results found by others in humans at page 53, lines 7-17. The model correlates to the course of the disease, continuous drug treatment, and interrupted drug treatment in humans.

The Prior Art

The Examiner states that Claims 22-24, 26 and 27 remain free of the prior art as they relate to administering antiretroviral drug therapy comprising ddI (an RI inhibitor) and indinavir (a protease inhibitor) until viral replication is suppressed, and then administering a DNA complex comprising a) DNA encoding an immunogenic retroviral protein operably linked with a promoter; and b) mannosylated polyethylenimine. The Examiner admits that the prior art did not teach or suggest administering ddI and Indinavir until viral replication is effectively suppressed, and then administering a gene delivery complex as claimed. The Examiner notes that Finzi (Science. Nov. 14, 1997, Vol. 278, pg 1295-1300) taught administering reverse transcriptase inhibitors and protease inhibitors to HIV patients. However, the Examiner further comments that Finzi did not relate to administering DNA encoding the marker protein luciferase to the brain of mice as taught by Boussif (PNAS, Aug. 1995, Vol. 92. pg 7292-7301) of record, administering DNA encoding a marker protein to cells in vitro as taught by Zanta (Bioconjugate Chem. 1997. Vol. 8. pg 839844) of record, administering DNA encoding a marker protein to cells in vitro as taught by Behr (US Patent 6,013,240) of record, or administering virus encoding integrase defective HIV to cells in vitro as taught by Cara (Virology, 1995, Vol. 208, pg 242-248).

The Examiner adds that the claims have not been searched far other antiviral drugs in combination with the gene complex as requested.

Response – The Prior Art

The Applicants note that, an appropriately framed search of the combination of Indinavir and ddI in combination with the claimed vaccine would also reveal the use of Indinavir or ddI individually with the vaccine. If such prior art has been found, the applicants respectfully request its disclosure, as being closer than any of the presently cited art. If there is any other prior art relating to the use of the applicant's vaccine in combination with any other drug treatment, the applicants respectfully request that it be disclosed to them as soon as possible.

Double Patenting

The Examiner states that Claims 28-31 remained rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,420,176 in view of the disclosure of 6,420,176 for reasons of record. The claims of 176 are said to be directed toward a gene delivery complex comprising DNA encoding an immunogenic protein operably linked to a promoter and mannosylated polyethylenimine. The Examiner admits that the claims of the '176 patent do not require administration as required in the instant claims or administration of antiretroviral drug therapy. The Examiner, however, points out that MPEP 804 states the specification may be used as a dictionary to learn the meaning of a term in the patent claim. In this case, one of skill would look to the specification to determine the asserted utility of the product. The disclosure taught administering the gene delivery complex after suppressing viral replication using antiretroviral drug therapy (col. 12, lines 11-51, see especially lines 20-27). Thus, the Examiner asserts that it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer the gene delivery complex in combination with drug therapy as claimed.

The Examiner states that the Applicants discuss what was desired in a vaccine but does not discuss why the parent application fails to teach one of skill to use the DNA to treat retroviral infection. The parent application states the DNA can be used to treat retroviral infection. Col. 12, line 19, does not indicate applicants "limitations of the use of the vaccine" because it states the DNA "can strengthen the immune [system]."

Applicants' discussion of the examiners response to previous arguments regarding "unexpected results" is moot (last paragraph on pg 14 of response). Applicants have not elaborated on the previous "unexpected results" arguments. The examiner was merely addressing applicants' misplaced "unexpected results" argument to the best of his ability.

The Examiner states also that Claims 28-31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending Application No. 10/081922 for reasons of record. Although the Examiner admits the allegedly conflicting claims are not identical, he states that they are not patentably distinct from each other because they overlap in scope. The Examiner states that the Applicants have not addressed this rejection.

Response – Double Patenting

In response, the Applicants note that the present application is a CIP of the cited patent, and is therefore inherently limited to the same term as the parent patent, because the term is controlled by the file date of the earliest priority document. The applicants have enclosed a Terminal Disclaimer for the parent patent, and note that the cited application is a division of the parent patent, with no claims allowed. The parent application is drawn to a vaccine. The present application contains significant additional

disclosure relating to drug treatments that can be used in combination with the vaccine, and experiments conducted subsequent to the filing of the parent patent, which yielded a new method of treating existing infection. The division of the parent patent is incapable of yielding claims that overlap with the claims that are currently being considered, because the divisional application does not contain disclosure that the Examiner will consider enabling disclosure relating to the use of the claimed method of using drug treatments in conjunction with the claimed vaccine. In the event this objection is not withdrawn, and for the purpose of expediting prosecution, the applicant has furnished a terminal disclaimer with respect to the application, together with an authorization to charge a deposit account.

Conclusion

It is believed that all the Examiner's legitimate concerns have been met, and that the Claims are in condition for allowance. Favorable consideration is solicited.

Respectfully Submitted,

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